CLAIMS

1. A method of making a set of labelled compounds, by the use of a support and a set of labels, which method comprises the steps:

a) at least one first or intermediate step comprising dividing the support into lots, performing a different chemical reaction on each lot of the support so as either to modify that lot of the support or to couple a chemical moiety to that lot of the support, tagging a fraction of each lot of the support with a different label, and combining the said lots of the support, and

b) at least one intermediate or final step comprising dividing the support into lots, performing a different chemical reaction on each lot of the support, so as either to modify that lot of the support or to couple a chemical moiety to that lot of the support, tagging a fraction of each lot of the support with a different cleavable label, whereby each different cleavable label is linked to a chemical moiety coupled to the support in a different step and forms with that chemical moiety a labelled compound which is separable from the support, and combining the said lots of the support.

2. The method of claim 1, wherein the support is a particulate solid support.

3. The method of claim 1 or claim 2, wherein step b) is performed to couple the chemical moiety to a chemical moiety previously coupled to the support.

4. The method of claim 3, wherein the chemical moieties are monomer units and the labelled compounds are oligomers.

5. The method of claim 4, wherein the set of labelled compounds is a library of n^s oligomers, where n is the number of different monomer units and s is the number of monomer units in each labelled oligomer, wherein step a) is performed once to couple a different monomer unit to each lot of the support, and step b) is performed s-1 times.

6. The method of claim 5, wherein the set of labelled compounds contains n x s different labels.

7. The method of any one of claims 1 to 6, wherein each labelled compound comprises a single label and at least one chemical moiety.

8. The method of any one of claims 1 to 7, wherein the support is treated to release the said labelled compounds into solution.

9. The method of any one of claims 1 to 8, wherein from 0.25% to 25% of each lot of the support is tagged in each step with a different label.

10. The method of any one of claims 1 to 9, wherein the support has cleavable linkers, wherein each cleavable linker has at least one group for chemical synthesis and another group for labelling.

11. The method of any one of claims 1 to 10, wherein the label is cleaved to give a charged species for mass spectrometry.

12. The method of any one of claims 1 to 11, wherein each label is a group of formula $R^1R^2R^3C$–, where R^1, R^2 and R^3 are the same or different and each is a monocyclic or fused ring aromatic group that is substituted or unsubstituted.

13. The method of claim 12, wherein at least one of R^1, R^2 and R^3 carries a substituent selected from C_1-C_{20} alkoxy or hydrocarbyl either unsubstituted or substituted by carboxylic acid, sulphonic acid, nitro, cyano, hydroxyl, thiol, primary, secondary or tertiary amino, primary or secondary amido, anhydride, carbonyl halide or active ester.

14. The method of any one of claims 1 to 13, wherein the labelled compounds are labelled oligonucleotides.

15. A set of labelled compounds wherein a molecule of a compound of the set is tagged with a single cleavable label which identifies the nature and/or the position of a component of that molecule, and different molecules of the same compound are tagged with different labels.

16. The set of claim 15, wherein the labelled compounds are releasably attached to a solid support.

17. The set of claim 16, wherein the solid support is particulate.

18. The set of claim 15, wherein the labelled compounds are mixed together in solution.

19. The set of any one of claims 15 to 18, wherein the label is cleaved to give a charged species for mass spectrometry.

20. The set of any one of claims 15 to 19, wherein each label is a

group of formula $R^1R^2R^3C$–, where R^1, R^2 and R^3 are the same or different and each is a monocyclic or fused ring aromatic group that is substituted or unsubstituted.

21. The set of claim 20, wherein at least one of R^1, R^2 and R^3 carries a substituent selected from C_1-C_{20} alkoxy or hydrocarbyl either unsubstituted or substituted by carboxylic acid, sulphonic acid, nitro, cyano, hydroxyl, thiol, primary, secondary or tertiary amino, primary or secondary amido, anhydride, carbonyl halide or active ester.

22. The set of any one of claims 15 to 21, wherein the labelled compounds are labelled oligonucleotides.

23. A library consisting of a plurality of the sets of any one of claims 19 to 22.

24. A reagent comprising a solid support which carries on its surface molecules of an oligomer, with different oligomer molecules having the same sequence wherein the oligomer molecules include some shorter oligomer molecules and a shorter oligomer molecule carries a label which identifies the nature and position of a monomer unit of the oligomer molecule.

25. The reagent as claimed in claim 24, wherein the solid support is a bead.

26. The reagent as claimed in claim 24 or claim 25, wherein the label is joined by a link that is photocleavable to give a charged species for mass spectrometry.

27. The reagent of any one of claims 24 to 26, wherein each label

is a group of formula $R^1R^2R^3C$–, where R^1, R^2 and R^3 are the same or different and each is a monocyclic or fused ring aromatic group that is substituted or unsubstituted.

28. The reagent of any one of claims 24 to 27, wherein at least one of R^1, R^2 and R^3 carries a substituent selected from C_1-C_{20} alkoxy or hydrocarbyl either unsubstituted or substituted by carboxylic acid, sulphonic acid, nitro, cyano, hydroxyl, thiol, primary, secondary or tertiary amino, primary or secondary amido, anhydride, carbonyl halide or active ester.

29. The reagent of any one of claims 24 to 28, wherein the oligomers are oligonucleotides.

30. A library consisting of a plurality of the reagents of any one of claims 24 to 29.

31. A method, which method comprises providing a labelled oligonucleotide or nucleic acid, and removing the label by cleavage to give a charged species which is subjected to matrix-free mass spectrometry.

32. The method of claim 31, wherein nucleic acid sequencing is performed by the use of a labelled primer and/or a labelled hybridisation probe and/or labelled chain extending nucleotides and/or labelled chain terminating nucleotide analogues, wherein the label is one which is removed by cleavage to give a charged species which is subjected to matrix-free mass spectrometry.

33. A reagent for an assay in which a labelled probe is partitioned into two fractions one of which is analysed, the probe comprising a ligand joined to a label by a link which is cleavable to give a charged species for matrix-free mass spectrometry.

34. The method of claim 33, wherein the ligand is an oligonucleotide.

35. The method of any one of claims 31 to 34, wherein the label is a group of formula $R^1R^2R^3C$–, where R^1, R^2 and R^3 are the same or different and each is a monocyclic or fused ring aromatic group that is substituted or unsubstituted.

36. The method of claim 35, wherein at least one of R^1, R^2 and R^3 carries a substituent selected from C_1-C_{20} alkoxy or hydrocarbyl either unsubstituted or substituted by carboxylic acid, sulphonic acid, nitro, cyano, hydroxyl, thiol, primary, secondary or tertiary amino, primary or secondary amido, anhydride, carbonyl halide or active ester.

37. A library of probes each comprising a ligand joined to a label by a link which is cleavable to give a charged species for analysis by mass spectrometry, wherein each different probe has a different label.

38. The library of claim 37, wherein the ligand is an oligonucleotide.

39. The library of claim 37 or claim 38, wherein each label is a group of formula $R^1R^2R^3C$–, where R^1, R^2 and R^3 are the same or different and each is a monocyclic or fused ring aromatic group that is substituted or unsubstituted.

40. The library of claim 39, wherein at least one of R^1, R^2 and R^3 carries a substituent selected from C_1-C_{20} alkoxy or hydrocarbyl either unsubstituted or substituted by carboxylic acid, sulphonic acid, nitro, cyano, hydroxyl, thiol, primary, secondary or tertiary amino, primary or secondary amido, anhydride, carbonyl halide or active ester.

41. A compound of formula $R^1R^2R^3CY$, where Y is a leaving group for reaction with a nucleophilic species, and R^1, R^2 and R^3 are the same or different and each is a monocyclic or fused ring aromatic group, at least one of which carries a substituent selected from $C_1 - C_{20}$ alkoxy or hydrocarbyl either unsubstituted or substituted by carboxylic acid, sulphonic acid, nitro, cyano, hydroxyl, thiol, primary, secondary or tertiary amino, primary or secondary amido, anhydride, carbonyl halide or active ester, provided that R^1, R^2 and R^3 together carry at least two amide groups and/or at least two N-hydroxysuccinimide ester groups.

42. The method of any one of claims 12, 13, 35 and 36, wherein $R^1R^2R^3C-$ is a substituted monomethoxytrityl group.

43. The set of claims 20 or 21, or the reagent of claim 27 or 28, or the library of claims 41 or 42, wherein $R^1R^2R^3C-$ is a substituted monomethoxytrityl group.

44. The compound of claim 41, wherein $R^1R^2R^3CY$ is a substituted monomethoxytrityl compound.

45. An insert for use as a target for laser desorption ionisation mass spectrometry, which insert has a planar target surface of glass or of an organic polymer bearing an immobilised compound for analysis, directly attached to said target surface.

46. The insert of claim 45, wherein the compound to be analysed comprises a group of formula $R^1R^2R^3C-$, where R^1, R^2 and R^3 are the same or different and each is a monocyclic or fused ring aromatic group that is substituted or unsubstituted.

47. The insert of claim 46, wherein at least one of R^1, R^2 and R^3 carries a substituent selected from C_1-C_{20} alkoxy or hydrocarbyl either unsubstituted or substituted by carboxylic acid, sulphonic acid, nitro, cyano, hydroxyl, thiol, primary, secondary or tertiary amino, primary or secondary amido, anhydride, carbonyl halide or active ester.

48. The insert of claim 46 or 47, wherein $R^1R^2R^3C-$ is a substituted monomethoxytrityl group.

49. The insert of any one of claims 45 to 48, wherein the target surface carries an array of immobilised compounds for analysis.

50. The insert of anyone of claims 45 to 49, wherein compounds are immobilised on target surfaces of glass by means of epoxysilane chemistry or isothiocyanate chemistry or mercaptosilane chemistry or polylysine.

51. A kit comprising a mass spectrometer and a supply of inserts bearing an immobilised compound for analysis directly attached to said insert surface, for use as targets for matrix-free laser desorption mass spectrometry, having target surfaces of glass or of an organic polymer.

52. A system for analysing nucleic acids comprising:

- a solid support carrying an array of nucleic acids to act as targets for analysis or as probes to capture a target;
- oligonucleotide reagents tagged with moieties suitable for analysis by mass spectrometry;
- reagents and apparatus for biochemical procedures to allow specific interaction between the tagged oligonucleotides and the target;
- a means to introduce the samples into a mass spectrometer;
- a mass spectrometer.

53. A system for analysing nucleic acids on a solid support comprising:

- a solid support carrying an array of nucleic acids to act as targets for analysis or as probes to capture a target;
- oligonucleotide reagents, tagged with moieties suitable for analysis by mass spectrometry;
- reagents and apparatus for biochemical procedures to allow specific interaction between the tagged oligonucleotides and the target carried out on the solid support surface;
- a means to introduce the solid support into a mass spectrometer;
- a mass spectrometer.

54. An automated system for analysing nucleic acids comprising:

- oligonucleotide reagents, tagged with moieties suitable for analysis by mass spectrometry;
- a mass spectrometer;
- a computer to carry out the analysis;

software to interpret a mass spectrum.

55. A nucleotide or oligonucleotide labelled with a tag suitable for analysis by mass spectrometry, said labelled nucleotide or oligonucleotide being suitable for enyzmatic incorporation, wherein the tag is a compound of formula $R^1R^2R^3CY$, where Y is a leaving group for reaction with a nucleophilic species, and R^1, R^2 and R^3 are the same or different and each is a monocyclic or fused ring aromatic group, at least one of which carries a substituent selected from C_1 – C_{20} alkoxy or hydrocarbyl either unsubstituted or substituted by carboxylic acid, sulphonic acid, nitro, cyano, hydroxyl, thiol, primary, secondary or tertiary amino, primary or secondary amido, anhydride, carbonyl halide or active ester.

56. The method of any one of claims 31 to 36, wherein 4s different labels are used, where the labelled oligonucleotide or nucleic acid contains s bases and each label is indicative of the position and identity of a nucleotide residue of the labelled oligonucleotide or nucleic acid.

57. The method of claim 56, wherein for a base position of the labelled oligonucleotide or nucleic acid, four regions of a mass spectrum corresponding to the masses of the four possible labels (including their isotopic variants) are examined and compared with an expected mass spectrum of the label.

58. The method of any one of claims 31 to 36, wherein each possible oligonucleotide or nucleic acid containing s bases is compared in turn against a mass spectrum comprising the s different tag regions, to identify the oligonucleotide having the best fit.

ADD A14